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WANDERING CELLS IN ANIMAL BODIES.

BY J. L. KELLOGG.

IF some of the surface sediment of a quiet fresh-water pond be examined under the microscope, one would very likely find a curious, colorless organism, containing a number of granules, and perhaps now and then a microscopic plant. A little observation will show this animal—for such it is—to be merely a mass of protoplasm which possesses the power of changing its shape by the protrusion of any part of its body in irregular branches, or thin, fine filaments. By means of these, it is able to move very slowly from place to place, forcing its way between particles of dirt which surround it, and also to take in solid food. This latter process is accomplished by a covering over or flowing about a piece of food by the thin, jelly-like body. When the food is thus covered over, the fluid protoplasm of the animal, which is called an amœba, is seen to possess the power of truly digesting the food which it holds. This process, taking place in a single unspecialized or undifferentiated cell, is called intracellular digestion.

The amœba is, in its structure, a single cell, comparable to any one of the myriads of cells that go to make up the body of one of the higher animals. These cells may lose, in a higher organism, the simple amœboid form, and assume complex shapes and functions in different parts of the body; generally losing, also, the power of movement. Many, however, retain the power of moving under proper stimuli,—as, for example, the cells that go to make up muscular tissue, where their united contraction causes movements of organs of which they may form a part. This movement is, of course, not voluntary with the cell; but there are certain cells, even in the bodies of the most highly differentiated animals, which still possess this power of acting voluntarily without external stimuli.

If a drop of blood be taken from the body of any of the vertebrated animals, with one or two exceptions, and the microscope again called into use, its fluid part will be seen to be filled with motionless, pale-yellow discs. Among these red blood corpuscles will be seen, here and there, transparent bodies, larger or smaller than these, as the case may be, which we recognize by their slow movement as amœboid cells. These are the white corpuscles of the blood. In lymphoid tissue, such as that of the spleen, and small lymph nodules occurring in different parts of the body, larger amœboid cells of the same nature are collected in great masses, which are richly supplied from the general vascular system. Though these amœboid cells in the blood are called white corpuscles, and in the lymph glands lymph corpuscles, and so on, they are all included in the general term "leucocytes." Their functions in these different tissues will be more readily understood if we first examine cells of the same nature in some of the lower forms of animal life; for in these their habits and relations to the bodies of which they are a part are more easily observed and classified.

The student of biology will recognize a distinct morphological bearing in the observations about to be recorded concerning these wandering cells. Our knowledge of them has come mainly through a study of the embryonic development of lower animals, and foremost among investigators of this subject must be placed the name of the great Russian morphologist, Metschnikoff. It was he who first noticed their similarity of function in the whole animal series, and he formulated his great mass of observations in what is called his phagocyte theory. Almost all the examples to be given here are the results of his researches. On account of their very great interest to all classes, these observations are very widely known, and we may briefly consider a few of them. In so doing, also, we will be better able to comprehend the important functions supposed to be possessed by amœboid cells in higher animals.

In the embryo of Echinoderms, such as the starfish, there is a stage in which the organism consists of a single layer of cells in the form of a sphere, called a blastosphere or blastula, and its interior is filled with a jelly-like mass. Certain of these cells in the layer work out from between their neighbors by amœboid movement, and come to lie free in this jelly (Fig. 1), where they move about. This is a fact of morphological interest, as these cells eventually form one of the primary layers—the germ-layers—of the embryo, which, by a definite development, form certain organs of the adult. As the starfish blastula becomes older, it reaches a stage in which certain of its tissues break down, and these are not to pass into the body of the adult animal. Metschnikoff has observed that broken-down particles were taken up by the moving cells, as the Amœba takes its food, and also found that they were digested by the cells. Now these particles, if allowed to remain, would have been injurious to the animal, so their assimilation by the amœboid cells was of great use to the individual. It was because of this peculiar function that the wandering cells were called phagocytes, or eating cells, and they are very generally known by this term.

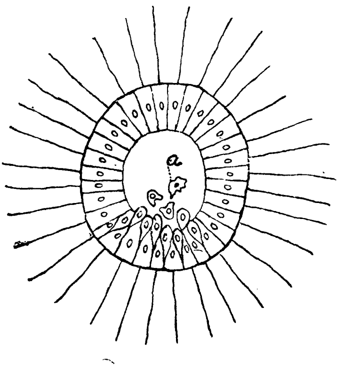

Fig. 1

Larva of Echinoderm which has begun to swim by means of cilia, showing amœboid cells.

In order to establish a theory, now generally accepted, of the descent of the Metazoa, or many-celled animals, from the Protozoa, or single-celled forms, Metschnikoff sought for and proved the existence of this intracellular digestion in certain amœboid cells of sponges. Following out these facts, obtained in purely morphological research, he was enabled to lay the foundation for certain views which are of the utmost practical interest, as we shall see, even in such an apparently remote field as that concerning many diseases of the human race.

In a tadpole, whose legs have commenced to grow, preparatory to assuming the adult condition, the tail begins to wither and disappear; and in this organ, Metschnikoff made another interesting and well-known discovery. The tissues were now of no further use to the organism, and he found that the leucocytes had attacked them, and were gradually eating them away. He often found unmistakable pieces of nerve and muscle-tissue inside their bodies, which were evidently undergoing a process of obliteration by digestion. In the pupa stage of insect metamorphosis the internal organs are disintegrated, and here again the phagocytes attack the useless tissues and eat them. Certain strong, well-nourished cells, however, remain unharmed, and from these the organs of the adult are built up.

Such an occurrence as this appears to be rather remarkable, and the question at once arises as to why these phagocytes should destroy one tissue, and apparently leave another uninjured. Metschnikoff has conclusively shown that these wandering cells exert an undoubted choice in the selection of their food, and that they prefer dead to living tissue. His method of proving this fact was as follows. Taking some sea-urchin's eggs, and killing them by boiling, he carefully injected them under the skin of a nudibranch,—one of the Gastropods,—and found that they were immediately surrounded by amœboid cells, and eaten by them in the usual manner. The same experiment was again tried, but this time the injected eggs were not killed. The result was that they not only remained unharmed, but, on the introduction of spermatozoa among them, they were fertilized, and commenced to develop.

In such an experiment as this, it is noticeable that when a foreign body is introduced into an animal through an injured region of the skin, the leucocytes already in the vicinity are not the only ones which are ready to attack the invading particles. Very soon their fellows appear, having come from distant tissues, and take part in the fray; and not only do they attack organic substances, which by digestion would be assimilated, but also inorganic particles, which they cover by their protoplasm, and retain, so that they cannot do harm to the animal. I have been told that in men whose arms have been extensively tattooed with India ink, the small lymph nodules in the axillæ are sometimes very deeply pigmented. As has been said, these nodules are made up principally of amœboid lymph leucocytes, and when the lymph, carrying particles of ink, passes through them, the phagocytes pick up the pigment granules and retain them.

Again, it has recently been stated that if a bit of sponge be inserted under the skin of any of the mammals it will in a few days entirely disappear; and if, before this occurs, it be taken out and examined, it will be found to be full of phagocytes which are destroying it.

Osler, in a recent address on the subject, says that in the sputum of smokers there appear cells from the alveolar epithelium of the lungs, which are evidently amœboid, carrying particles of carbon. The same is said to be the case with miners who inhale coal-dust, and that these carbon-laden cells may continue to appear for months after a man has ceased to expose himself to the dust. It need not be said that such unusual work put upon the lungs might lead to serious results.

In the process of digestion in mammals, fats are emulsified, or broken into small particles in the intestine, and are transferred bodily through its wall into lymph vessels. In this it differs from the transfer of a dissolved salt through a membrane by dialysis, and the numerous leucocytes in the intestinal wall are known to carry the fat particles through the lining epithelium into the lymph capillaries beneath, where they disintegrate and liberate their load. It is not definitely understood how the fat particles are taken in, but it is supposed that the phagocytes push out processes or pseudopodia to the surface of the stationary epithelium cells, and then surround them, and draw them inward.

There seems to be a tendency to divide the functions of leucocytes into those which are normal, and abnormal. For example, in the last instance mentioned, the work done by amœboid cells is said to a natural or normal one, and it undoubtedly is so. On the other hand, the attack made upon the bit of sponge introduced beneath the skin would by some be called an abnormal function performed by the wandering cells. It would seem, however, that a tissue so constructed as to be able to adapt itself to conditions caused by some unforeseen accident would employ an entirely normal function in adapting itself to new circumstances. An irritating particle may be placed between the shell and mantle of an oyster, and very soon the cells of the latter secrete a hard covering of pearl over the foreign object. The secretion would not have taken place had it not been for this accident, and yet we regard the process as an entirely normal one. In the case of the collecting of dust particles in the alveoli of the lungs, some may call it a natural function, while others may have a different opinion. The leucocytes in animal bodies, though they may differ from one another in some respects, are essentially alike in function as far as is known, and anything that they are called upon to do, and are able to perform, may be regarded as normal.

One more fact concerning the action caused by the introduction of foreign, inorganic bodies is that, if the substance be too large, the leucocytes often unite with one another and cover the object. They make a fixed covering of what is called fibrous tissue, and the process is known as encystment. Sometimes, however, great numbers of leucocytes may die in the attempt to dispose of foreign particles, and their disintegrated bodies form a substance called pus. The sore resulting from this is an abscess.

We shall now see that these leucocytes have a far more interesting and important function than those already mentioned, and its discovery was made by Metschnikoff. It is known to every one that a number of diseases to which man and other mammals are subject are caused by bacteria,—microscopic plants,—which enter the body in various ways, and by their multiplication occasion changes in the tissues that may be exceedingly dangerous to the attacked individual. It is claimed by many, that the most important function of the phagocytes is to take up these micro-organisms and destroy them.

Perhaps the most interesting observation given us on this subject by Metschnikoff is that made upon Daphnia, a small fresh-water crustacean. He found that many of these animals, which he kept in an aquarium, were very liable to be attacked by the long, needle-like spores of a certain fungus. These, once established in the tissues, multiplied and often caused the death of the animal. The spores first obtain a position in the intestine. By degrees they work their way through its walls, and appear in the body-cavity. As soon as this happens, phagocytes appear on the scene in great numbers, and attack the invaders. If these can only be killed, they will be rendered harmless, for then their breaking down can be accomplished, and they can be removed. But if they are too numerous, some will escape uninjured, and, finding themselves under suitable conditions, will sprout and grow, and this means the death of the individual. It will be seen by Figure 2 that one of these spores is several times larger than a leucocyte, and though the latter is capable of great distension, it may not be able alone to dispose of a spore. In such a case, two or more may invest different parts of the same enemy. But a more effectual coöperation may be secured in this remarkable way. Several cells may become fused into one great mass, forming a single individual of sufficient size to surround a spore and kill it. When this has been accomplished, the spore soon loses its original shape, and finally falls to pieces. These different stages are shown in Figure 2. This united effort of the phagocytes may thus prevent disease; though very often, when the invasion is too great, they are not able to stem the tide, and the animal dies.

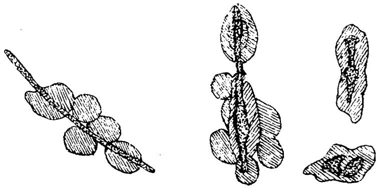

Fig. 2

Spores and blood corpuscles from the body-cavity of Daphnia. After Metschnikoff.

Still following, for the present, the experiments of Metschnikoff, we may notice a few observations made upon vertebrates. The microörganism of splenic or relapsing fever is a large bacillus, and favorable for study on this account, for bacteria appear as extremely small objects, even when magnified as greatly as possible. Taking a bit of infected tissue from an animal suffering from this disease, Metschnikoff placed it under the skin of a mammal, such as a mouse or rabbit, and on taking it out and examining it, in the course of a few hours, he found that it had been surrounded by the wandering cells of the animal, and that many of the bacilli had been taken up, and appeared to be undergoing a process of digestion in their interior (Fig. 3). Of course, it often happens that in animals suffering from this disease, the bacilli may become so numerous as to kill the amœboid cells, and finally cause the death of the animal itself.

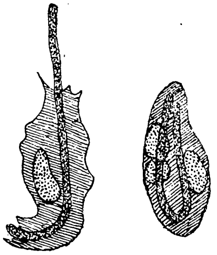

Fig. 3

Leucocytes from a frog, taking up the bacilli of splenitis. After Metschnikoff.

It is well known that in typhus fever there are certain stages of the disease in which great numbers of spirilla—another form of bacteria—are found in the blood of the suffering individual. Now one would naturally expect, from what has been stated, that the white blood corpuscles would be found to contain them; but, curiously enough, this is seldom, if ever, found to be the case. In making experimental investigations with the prevention of this disease in view, Metschnikoff recognized in this fact a serious objection to the theory which he had advanced concerning these leucocytes. He inoculated an ape with the spirilla, and they soon appeared in the blood. Some time afterward, however, they became less numerous, and finally disappeared altogether. This circumstance led Metschnikoff to suspect that perhaps they had collected in some other part of the body, so he killed the ape, and finally found that the amœboid cells of the spleen were filled with the missing spirilla. To be sure, some were yet free, but a great many were not only invested, but in all stages of digestion. This fact throws some light on the unknown function of the spleen, and at least indicates the conclusion that it attains to the importance of a therapeutic organ.

In erysipelas there is not only an acute inflammation, but also a degeneration of tissues; and it has been for some time an unexplained fact that a resorption of these broken-down parts took place. The disease is caused by the penetration of a streptococcus; and Metschnikoff found that there were here two kinds of amœboid cells at work, one of which, the smaller, attacked the cocci in the usual manner, while the other concerned itself only with the taking up of tissues which had been broken down in necrosis.

We have here an interesting array of facts, which have been graphically summed up by Osler. He says that Metschnikoff has likened specific inflammation to a warfare in which the invading forces are represented by microörganisms, and those who offer resistance by leucocytes. The news of the arrival of an enemy is telegraphed to headquarters by the vaso-motor nerves, and the blood vessels are used as an avenue of communication with the threatened region. When the invaders are established, they live on the host, and scatter injurious substances which they have formed. The active leucocytes make an attack, and try to eat the microörganisms, and some may die in the fight. Their dead bodies form an accumulation of pus, and when many are slain, the battle-ground is known as an abscess. Either force may be victorious, resulting in the one case in the recovery of the animal, and in the other in its sickness or death. In our bodies, then, there is a standing army of movable cells, which may be quickly concentrated, and attack any foreign foe which may appear.

With a view of determining how active the phagocytes actually were in attacking foreign bodies, C. Hess took a small glass receptacle, on the side of which was a very fine slit opening into its interior. He now filled this glass with a pure culture of whatever microörganism he chose to use, and, leaving the slit open, he placed it beneath the skin of a dog or pigeon. This foreign body very soon caused an inflammation. After some time, Hess found that a multitude of wandering cells had collected about the glass, and upon removing it, he found that a great number of them had worked their way through the opening into its interior, and were then actively engaged in a battle with the bacteria. He did not stop here in his observations, however, but continued to watch the movements of the phagocytes, and finally came to the conclusion that the invested plants were destroyed by a true process of intracellular digestion.

Sutton has recently given some valuable information in regard to tuberculosis in birds, which he says is more prevalent than in man. He tells us that the bacilli, from whatever place they may have come, get into the alimentary canal, and there penetrate into its walls. In some cases they may be taken up in the blood vessels, and getting into the general circulation, may finally be deposited in distant tissues of the body, such as the liver, lungs, or brain, and, in multiplying, cause the death of the animal. In the bowels, they are undoubtedly attacked by the leucocytes, and are surrounded, killed, and destroyed. Sometimes the battle may go against the defending force, when the bacilli are gaining an entrance, and then great numbers gather to reinforce their comrades. Many are killed, forming pus-cells, and others fuse together, as Metschnikoff saw them doing about the spores in Daphnia, and forming the giant cells. "These giant cells," says Sutton, "are powerful antagonists, for I have seen one contain as many as fifty bacilli."

The relation of leucocytes to inflammation and fever is pretty generally admitted. It is easily demonstrated that, under certain stimulation, such as the exposure of a bit of the mesentery of an animal, or the introduction of some foreign body, the leucocytes appear on the spot, coming in blood vessels from distant parts; and that they, in some way, penetrate the vessel walls, and appear in the tissue outside, ready to engage an enemy which may be present. As the last author referred to says: "Zoologically considered, inflammation is, in essence, a local struggle between irritants and the white cells of the blood. When the whole of the blood is engaged in the struggle, as in ague, anthrax, and the like, we have general inflammation or fever. The different varieties of fever, when due to microörganisms, depend on the habits of specific bacteria; some are more virulent, others are slower in attaining maturity, or are more irritating to the tissues."

There is something wonderfully attractive in this theory of Metschnikoff's, and of course when it became known, a great number of investigators at once began to make all kinds of experiments bearing on the question. Many have confirmed the theory, but there are also those who bitterly oppose it, and among such there are a few very prominent scientists.

Before saying anything about this other side of the question, it may be of interest to depart from the subject for a moment, and notice a few important facts in regard to the supposed micro-organisms of disease.

Different species of bacteria—using the term to include all micro-organisms—appear everywhere in great numbers ; but they are not all to be dreaded as enemies of mankind. When an animal dies its body is disintegrated and returns to dust by their action. Not only is this the case, but some species are actually of great benefit to our living bodies, by helping to carry out the functions of some of its organs. Some time ago, however, the presence of certain specific microörganisms was noticed to be of constant occurrence in certain diseases, while they were absent in a normal condition. The discovery was an interesting one. Investigations multiplied, and finally a great number of diseases were believed, by some, to be caused by these so-called "germs." It made little difference whether or not there was any other reason for it than the presence of some form in the course of the disease, which was supposed to be its cause. Finally conservative men saw the danger of allowing this unsound reason of *post hoc, ergo propter hoc*, to carry things any farther. Better reasons for the prevailing belief were asked for, and generally failed to be given. Almost everything was then received with doubt, and to-day the pendulum of popular belief in the subject seems to have swung very far in the opposite direction. This is evidenced in a statement by Dr. Koch, the great German bacteriologist, who has recently created such an interest through the world by his supposed cure for consumption. In a recent address before the International Medical Congress, he says that but three microörganisms are positively proven to be the causes of disease: namely, those of anthrax, erysipelas, and tuberculosis. Other great authorities, however, would add a few more, such as those causing glanders, cholera, pneumonia, and so on. At any rate, the number is now surprisingly small. Variations of the theory are now being suggested. Some believe that certain diseases may be caused by a combination of many kinds of microörganisms. The opinion seems to be growing that ordinarily harmless, or septic, forms may, under favorable conditions, change into those which are harmful, or pathogenic.

It is probable that most people, or at least those living in great cities, take into their bodies daily, micro-organisms which, under very favorable conditions, would cause disease. One person may take in safely, perhaps, many times the number required to cause disease in another. Sutton has expressed this fact as follows: "The more these questions are studied, the more we perceive that the outbreak of infectious diseases depends not so much on the presence of microörganisms—for, like torula (the yeast plant), they seem to exist everywhere—as upon the existence of suitable conditions, and as yeast cannot grow and multiply without sugar, neither can the poison of erysipelas, typhus fever, and the like propagate without the presence of some substance produced in living bodies, of the nature of which we are ignorant." For example, "relapsing fever is unknown except in times of famine, when the body-chemistry is deranged by want of food, privation, and hardships of every kind."

But to return to the phagocytes, we must notice a few objections that have been urged against the experiments of Metschnikoff. A few investigators who do not believe in the phagocyte theory, claim that there are other elements in the body which exert an active influence against microörganisms; but, of course, this, in itself, is no argument against the supposed function of the wandering cells. Ribbert, and one or two others, while agreeing with Metschnikoff on some points, believe from their experiments that such fungi as microörganisms, or spores of fungi, are prevented from growing in a tissue, not so much on account of an active attack of leucocytes, as the fact that the latter probably deprive them of oxygen necessary to their growth, and perhaps also keep away other nourishing materials. It seems to be impossible for any one to contradict, in any case, the fact that the phagocytes take up bacteria, unless in the instance referred to of splenic fever, when in the blood, this does not occur, as Metschnikoff himself found. But Flügge, and others, claim that the parasites taken up are really only those which have already been killed, or at least injured, by chemical substances of the body, and that the white blood corpuscles are simply scavengers that pick up dead material, as the lymph corpuscles are known to destroy feeble and broken-down red blood corpuscles in the spleen.

In experimenting with the anthrax bacillus, Baumgarten found that after having been injected into pigeons, the bacilli were very seldom taken up by leucocytes, but that they seemed to degenerate precisely as they did when left in distilled water. A great many objections have been of the nature of a direct contradiction of the observations which Metschnikoff claims to have made. For instance, it is stated by Koch that anthrax bacilli, though taken up in leucocytes, may actually continue to grow there. There are a great many bitter opponents of this eating-cell theory, and, no doubt, many observations have been made which would be very difficult to explain by it.

It is apparent from what has been said, that in spite of these objections, many facts remain, which are of great importance to the study of pathology and therapeutics. It will be of value, also, to the medical practitioner to keep himself informed on the progress of this work at the present day.

It is often asked by those who are not able to understand the true aim of a science, what practical results are obtained by the great search for unknown facts that is being made in the so-called natural sciences. Without mentioning the discoveries made in this way, which have successfully answered many economic questions, it is a noticeable fact that all the knowledge developed by this phagocyte theory, and the work it has stimulated, sprang, in the first place, from Metschnikoff's purely morphological researches.

If the knowledge obtained from the experiments here enumerated, cannot be directly applied to the relief of human suffering, it is probable that a foundation has been laid, upon which it may be possible to build up methods for operation against the common enemy.